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Pesticide Fact Sheet Number 127: EPN

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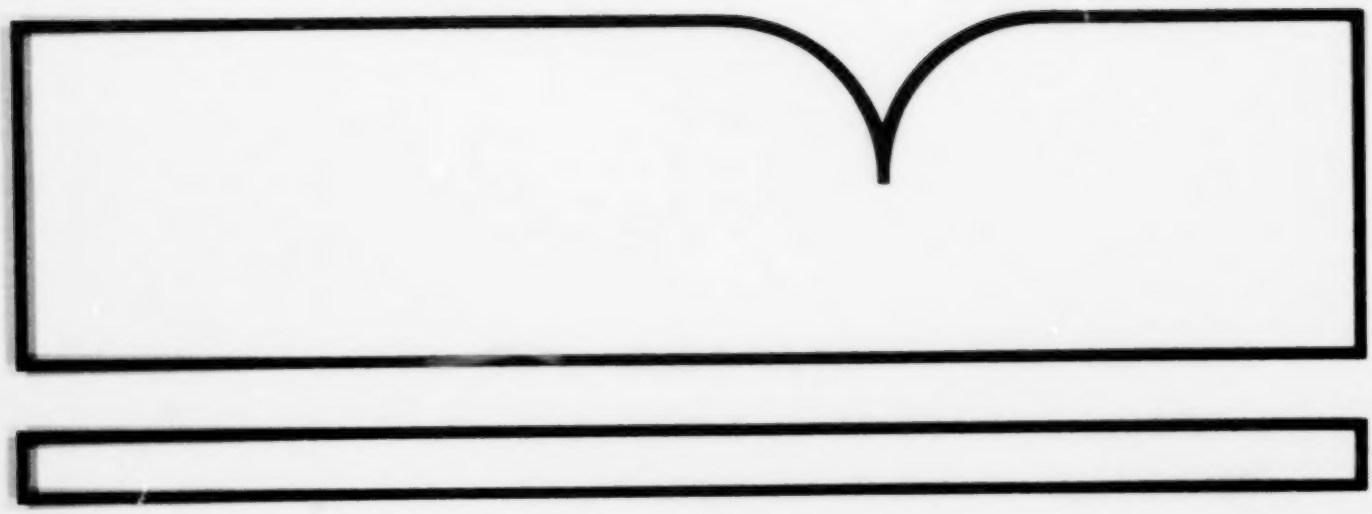

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This document contains up-to-date chemical information, including a summary of the Agency's regulatory position and rationale, on a specific pesticide or group of pesticides. A Fact Sheet is issued after one of the following actions has occurred.

1. Issuance or reissuance of a registration standard,
2. Issuance of each special review document,
3. Registration of a significantly changed use pattern,
4. Registration of a new chemical, or
5. An immediate need for information to resolve controversial issues relating to a specific chemical or use pattern.

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Pesticides, regulations, Chemical Information Fact Sheet, Use Patterns, Science Findings

b. Identifiers/Open-Ended Terms

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EPA

Pesticide Fact Sheet

Name of Chemical: EPN
Reason for Issuance: Issuance of Guidance Document
Date Issued: APR 30 1987
Fact Sheet Number: 127

1. DESCRIPTION OF CHEMICAL

Generic Name: O-ethyl O-p-nitrophenyl phenylphosphonothioate

Common Name: EPN

Trade and Other Names: None

EPA Shaughnessy Code: 041801

Chemical Abstracts Service (CAS) Number: 2104-64-5

Year of Initial Registration: 1949

Pesticide Type: Insecticide

Chemical Family: Organophosphate

U.S. and Foreign Producers: Nissan Chemical Works, Ltd. of Japan

There are no U.S. producers and there are no U.S. registrations for technical EPN. There were 32 end use EPN products registered in the U.S. as of April 29, 1987.

2. USE PATTERNS AND FORMULATIONS

Application Sites: Cotton, soybeans, field corn, pecans, almonds, apples, apricots, beans (green beans, lima beans, navy beans red kidney beans, snap beans), black-eyed peas, cherries (sweet and sour), citrus (citron, grapefruit, lemons, limes, oranges, tangelos, tangerines), corn (sweet), cowpeas, grapes, kumquats, nectarines, olives, peaches, pears, pecans, plums, prunes, sugar beets, tomatoes, walnuts, and earthworm farms.

Types and Methods of Application: Foliar broadcast using aerial or ground equipment.

Application Rates: Recommended application rates range from 0.125 to 5.0 pounds of active ingredient per acre.

Types of Formulations: Emulsifiable concentrates; granular; wettable powder.

3. SCIENCE FINDINGS

Summary Science Statement

EPN is a non-halogenated, aromatic, phosphonothioate organophosphorus compound with high acute toxicity. A single oral dose of the chemical has been shown to produce organophosphate type delayed neurotoxicity in the domestic hen. EPN has been shown to be non-teratogenic. Based on all mutagenicity tests reviewed, EPN is considered to be non-mutagenic although EPN technical was weakly mutagenic in a single replicate of one of the tests utilized. Data gaps exist for chronic feeding, oncogenicity, and reproduction. EPN is highly toxic to aquatic organisms and birds. Tolerances have been established for a number of raw agricultural commodities, however additional data are required to support many of them. The theoretical maximum residue contribution (TMRC) for EPN is 0.9859 mg/kg/day. A provisional acceptable daily intake (PADI) of 0.00001 mg/kg/day has been calculated for EPN based on the most sensitive study for delayed neurotoxicity, a 90-day oral dosing study in the hen with a NOEL of 0.01 mg/kg/day for irreversible histopathological changes in the spinal cord. This effect has been identified as the most sensitive indicator of EPN toxicity. The maximum permissible intake (MPI) for EPN is calculated as 0.0006 mg/day for a 60 kg person. Based on these figures and actual residue data for 5 representative crops, the TMRC occupies 120% of the PADI (using the percent of the crop treated in the calculation). Applicators, mixer/loaders and field workers (making early reentry into treated areas) are primarily acutely exposed to EPN during their work activities. Based on average exposure values from surrogate pesticide studies, the Agency calculated the daily margin of safety for applicators to be 0.05 for cotton, 0.01 for soybeans, and 1.4 for field corn. Margins of safety for field workers, based on dislodgeable residue dissipation data for EPN and no protective clothing, were calculated to be 30 at 7 days after application to cotton; 30 at 2 days after application to soybeans, corn, and pecans; and 30 at 35 days after application to citrus. Certain uses of EPN also have sufficient exposure to pose a potential hazard to certain endangered and/or threatened species of mammals, birds, aquatic organisms, crustaceans, reptiles and insects. EPN is slightly persistent; however, insufficient data are available for the Agency to fully assess the environmental fate and transport of the compound.

Chemical Characteristics of the Technical Material

Physical State: Oily liquid (technical); crystalline powder (pure).

Color: Reddish-yellow (technical); light-yellow (pure).

Odor: Aromatic odor.
Molecular weight and formula: 323.3 - $C_{14}H_{14}NO_4P_5$.

Melting Point: 34.5°C.

Vapor Pressure: 0.03 mmHg at 100°C (technical).

Specific Gravity: 1.27 at 20°C.

Solubility in various solvents: Miscible with benzene, toluene xylene, acetone, isopropyl alcohol, and methanol; slightly soluble in in water.

Toxicology Characteristics

Acute Oral: High acute oral toxicity to mammals with toxicity values of approximately 52.8 mg/kg/body weight in male rats and 13.2 mg/kg/body weight in female rats.
Toxicity Category I.

Acute Dermal: 354 mg/kg/body weight in male rabbits and 500 mg/kg/body weight in female rabbits.
Toxicity Category II.

Primary Dermal Irritation: Technical EPN does not produce dermal irritation.
Toxicity Category IV.

Primary Eye Irritation: Technical EPN does not produce eye irritation
Toxicity Category IV

Skin Sensitization: Data gap.

Acute Inhalation: Extremely acute inhalation toxicity with values of 0.076 mg/L in male rats and 0.024 mg/L in female rats
Toxicity Category I

Major routes of exposure: Dermal exposure, with some inhalation exposure, to applicators.

Delayed neurotoxicity: EPN causes organophosphate-type delayed neurotoxic effects in test animals. Histopathological changes were seen at 0.1 mg/kg/day; clinical effects (ataxia) were seen at 2.5 mg/kg/day.

Oncogenicity: Data gap.

Chronic Feeding: Data gap.

Metabolism: Partial data gap. Data presently available to the Agency show the existence of several possible metabolites, however, these metabolites were not identified. Further work must be performed to identify the metabolites of EPN.

Teratogenicity: EPN is not teratogenic.
Reproduction: Data Gap.

Mutagenicity: EPN is not considered to be mutagenic based on all of the mutagenicity tests reviewed, although EPN technical was weakly mutagenic in a single replicate of one of the tests utilized.

Physiological and Biochemical Characteristics

Mechanism of Pesticidal Action: Cholinesterase inhibition following contact with, or ingestion of, EPN treated surfaces.

Metabolism and Persistence in Plants and Animals: Available data indicate that EPN is slightly persistent, however, these data are insufficient to fully assess the transport of EPN. Although the metabolism of EPN in plants is not adequately understood, detailed characterization of residues in whole, 10-week old cotton plants has revealed the presence of EPN and two metabolites, O-ethyl phenylphosphonic acid and phenylphosphonic acid. This study also revealed that ^{14}C-residues of [^{14}C] EPN are absorbed into plant tissues following foliar application. Submitted data pertaining to the metabolism of EPN in animals indicate that EPN residues will transfer to tissues of poultry, but otherwise are inadequate to show the nature of those residues in poultry or other animals.

Environmental Characteristics

Available data are insufficient to fully assess the environmental fate and transport of EPN and the potential exposure of humans and nontarget organisms to EPN. Data gaps exist for nearly all applicable studies. However, available preliminary information indicate general trends of EPN behavior in the environment. EPN is slightly persistent and degrades in aerobic sandy loam soil with a half-life of 4 to 8 weeks. Phenyl phosphonic acid, O-ethyl phenyl phosphonic acid, and O-ethyl phosphonothioic acid are expected to be the main degradates under aerobic conditions. Data currently available are insufficient to characterize EPN's leaching potential for contamination of ground water. Data to characterize the potential of EPN to contaminate groundwater are being required. Treated

areas should not be re-entered for at least 7 days for corn or cotton crops, 35 days for citrus, and 2 days for all other crops, unless protective clothing is worn

Ecological Characteristics

Avian acute toxicity: LD_{50} values of 7.09 to 27 mg/kg for mallard duck; 53.4 mg/kg for ring-necked pheasants, and 5.25 mg/kg for coturnix.

Avian dietary toxicity: 8-day Dietary LC_{50} values of 168 ppm in mallard duck and 349 ppm in bobwhite quail.

Freshwater fish acute toxicity: 96-hour LC_{50} values ranged from 80 ug/L for rainbow trout to 190 ug/L for bluegill.

Marine fish acute toxicity: 96-hour LC_{50} values ranged from 37 ug/L for Spot to 140 ug/L for Sheepshead.

Freshwater invertebrate toxicity: 48-hour LC_{50} values ranged from 0.32 ug/L for Daphnia magna to 36.0 ug/L for Gammarus lacustris.

Marine invertebrate toxicity: 96-hour LC_{50} values ranged from 4.6 ug/L for Penaeus Stylirostris to 13.0 ug/L for Mysidopsis bahia.

TOLERANCE REASSESSMENT

Tolerances have been established for residues of EPN in a variety of raw agricultural commodities (40 CFR 180.119). The Agency has evaluated the residue and toxicology data supporting these tolerances and has determined that a full tolerance reassessment for EPN cannot be made at this time because of extensive residue chemistry and toxicology data gaps. Because of these extensive data gaps, no significant new uses, including group tolerances, will be granted until the Agency has received data sufficient to thoroughly evaluate the dietary exposure to EPN. (The Agency has actual residue data for five crops: soybeans, drybeans, tomatoes, corn and cotton. Taking the percent of crop treated into account, the Agency believes that it is unlikely that EPN residues on crops will be present at the tolerance levels listed.

The present United States tolerances and Mexican tolerances are listed below. No Canadian tolerances or Codex MRLs have been established for EPN.

Summary of Present EPN Tolerances

Commodity	Tolerance (ppm) United States	Mexico
Apples	3.0	3.0
Apricots	3.0	---
Beans	3.0	3.0
Beets	3.0	---
Beet greens	3.0	---
Blackberries	3.0	---
Boysenberries	3.0	---
Cherries	3.0	---
Citrus fruits	3.0	3.0
Corn	3.0	3.0
Dewberries	3.0	---
Grapes	3.0	3.0
Lettuce	3.0	3.0
Loganberries	3.0	---
Nectarines	3.0	---
Olives	3.0	---
Peaches	3.0	3.0
Pears	3.0	3.0
Pineapples	3.0	3.0
Plums (fresh prunes)	3.0	---
Quinces	3.0	---
Raspberries	3.0	---
Rutabagas	3.0	---
Rutabagas tops	3.0	---
Spinach	3.0	3.0
Strawberries	3.0	3.0
Sugarbeet tops (but not sugar beet tops)	3.0	---
Tomatoes	3.0	3.0
Turnips	3.0	---
Turnip greens	3.0	---
Youngberries	3.0	---
Almonds	0.5	---
Cottonseed	0.5	0.5
Pecans	0.5	---
Walnuts	0.5	---
Soybeans	0.05	0.05
Nuts	---	0.5

The data for EPN residues in or on beans (dried), cottonseed, tomatoes, and corn are adequate to support the respective established tolerances. However, the Agency requires that the tolerance for residues in or on corn be changed to two tolerances, each at 3 ppm, for residues in or on field corn grain and sweet corn (kernels plus cob with husks removed) and that the tolerance for residues in or on beans be changed to three tolerances for residues in or on dried beans at 3 ppm, and lima and snap beans for which additional data are required.

Data are not adequate to support the established tolerance for residues in or on almonds, apples, apricots, beans (snap and lima only), cherries, citrus, grapes, lettuce, nectarines, olives, peaches, pears, pecans, plums, soybeans, sugar beets (without tops), and walnuts.

There are currently no registered use for the following crops for which tolerances are established: beets and beet greens, blackberries, boysenberries, dewberries, loganberries, pineapples, quinces, raspberries, rutabagas, spinach, strawberries, turnips and turnip greens, and youngberries. The Agency will revoke the currently established tolerances for these raw agricultural commodities, unless the registrant submits usage proposals and the required data to support the tolerance.

The Agency will also move to revoke the tolerance for residues of EPN in or on rutabaga tops since rutabaga tops are not presently considered a raw agricultural commodity of rutabagas and no registered use of EPN on rutabagas exists.

The theoretical maximum residue contribution (TMRC) for EPN is 0.9859 mg/kg/day. A provisional acceptable daily intake (PADI) of 0.00001 mg/kg/ day has been calculated for EPN based on the most sensitive study for delayed neurotoxicity, a 90-day oral dosing study in the hen with an LEL of 0.1 mg/kg/day for histopathological evidence of toxicity in the spinal cord, a NOEL of 0.01 mg/kg/day and a safety factor or uncertainty factor of 1000. Histopathological changes in the spinal cord have been identified as the most sensitive indicator of EPN toxicity. The maximum permissible intake (MPI) for EPN is calculated as 0.0006 mg/day for a 60 kg individual. Based on these figures the TMRC is equivalent to 164,000% of the PADI. However, the Agency believes that this figure is actually much lower. For five crops for which the Agency has actual field residue data, the TMRC occupies 120% of the PADI, assuming the appropriate percent of crop treated for each crop.

4. Required Unique Labeling and Regulatory Position Summary

The Agency is initiating a Special Review for all registered uses of EPN based on the results of the delayed neurotoxicity studies, and the risks to the public from consumption of food commodities containing EPN residues and risks to workers involved with EPN application and working in fields treated with EPN. The use of EPN meets or exceeds the criteria for adverse effects (40 CFR 154.7 (a)(2)).

The Agency previously reviewed EPN in the special review process in 1979 when a Notice of Rebuttable Presumption Against Registration was issued (44 FR 54384) based upon studies showing that EPN caused delayed neurotoxic effects in test animals, and was acutely toxic to aquatic organisms. The Agency concluded that special review with publication of its final notice of determination in the Federal Register on August 31, 1983 (48 FR 39494) announcing:

- the cancellation of the mosquito larvicide use of EPN;
- the prohibition of the use of human flaggers during aerial application of EPN unless the flaggers were in totally enclosed vehicles;

- the requirement for standardized labeling statements for the use of protective clothing;
- the requirement for labeling statements regarding drift of EPN from treated areas; and
- the requirement for labeling statements warning of the hazard of EPN application to crops visited by bees.

The previous special review of EPN relied primarily on the NOEL of 0.1 mg/kg/day for EPN-induced depression of plasma and red blood cell cholinesterase levels in humans as the NOEL for delayed neurotoxicity. On that basis, the Agency calculated dietary and applicator risks posed by continued uses of EPN. The Agency concluded at that time that adequate margins of safety existed for human dietary exposure and for applicators with the exception of flaggers.

Information received since that time on various cholinesterase-inhibiting compounds indicates an effect on blood cholinesterase is not the most sensitive indicator of toxicity for organophosphates. New information on recovery after a single large dose of EPN in hens indicates that the spinal histopathological changes are a more sensitive indicator of toxicity and that these changes are irreversible. This finding has led the Agency to conclude that the most appropriate NOEL to use for risk assessment purposes and the most sensitive indicator of potential human toxicity for this histopathological effect is 0.01 mg/kg/day from a 90-day subchornic feeding study in hens.

No significant new uses, including group tolerances, will be granted until the Agency has received data sufficient to thoroughly evaluate the dietary exposure to EPN.

The Agency is continuing the restricted use classification of all liquid formulations and any formulation greater than 4 % EPN. Application must be made by, or under the direct supervision of, Certified Applicators. Direct supervision for EPN products is defined as the Certified Applicator being physically present during mixing, loading, equipment repair, and equipment cleaning. Applicators must ensure that all persons involved in these activities under their direct supervision are informed of the precautionary statements.

The Agency is requiring a label statement concerning the histopathological changes in the spinal cord to be used in conjunction with the restricted use statement.

Endangered species labeling will be required at a later date for certain use patterns of EPN. Specific labeling requirements will be imposed through a Pesticide Registration (PR) Notice.

Preliminary evaluation of recently submitted toxicity and dissipation data indicate that the 24-hour reentry interval established in 1974 for EPN under 40 CFR 170.3 (b)(2) does not provide adequate protection for field-workers. Therefore, until the Agency receives acute delayed neurotoxicity data on which to base the risk assessment to determine the most effective

reentry interval for EPN, the Agency is requiring the following reentry intervals: 7 days for corn and cotton; 35 days for citrus; and 2 days for all other crops.

Work safety rules, precautionary statements, and protective clothing statements for mixer/loaders and applicators are required to be included on the label of EPN products.

All EPN end-use product labeling is required to contain work safety rules, precautionary statements, and protective clothing statements.

The Agency is requiring processing data for the following raw agricultural commodities: sugar beets, soybeans, tomatoes, citrus, prunes, grapes, apples, cottonseed, corn, and olives.

The Agency is requiring the addition of the telephone number of the National Pesticide Telecommunications Network to all end-use EPN products.

While data gaps are being filled, currently registered manufacturing use products and end use products containg EPN may be sold, distributed, formulated, and used, subject to the terms and conditions specified in the Registration Standard for EPN. Registrants must provide or agree to develop additional data in order to maintain existing registrations.

5. Summary of Major Data Gaps

Toxicology

Acute delayed neurotoxicity - single dose NOEL
Dermal sensitization
Chronic toxicity (two species - rodent and non-rodent)
Oncogenicity study (two species - rat and mouse preferred)
Reproductive study
Metabolism

Environmental Fate

Hydrolysis
Photodegradation, water
Photodegradation, soil
Aerobic metabolism
Anaerobic metabolism
Leaching and adsorption/desorption
Soil dissipation
Long-term soil dissipation
Rotational crop (confined)
Rotational crop (field)
Fish accumulation
Droplet size spectrum
Spray drift field evaluation

Eclogical Effects

Avian reproduction study
Fish early life-stage study
Aquatic invertebrate life-cycle study
Aquatic monitoring or mesocosm study

Residue Chemistry

Storage stability study
Plant metabolism study
Animal metabolism study
Residue data for almonds, apples, apricots, beans (snap and lima), cherries, citrus, grapes, lettuce, nectarines, olives, peaches, pears, pecans, plums, soybeans, sugar beets (without tops), and walnuts.
Residue data and usage proposal for beets and beet greens, blackberries, boysenberries, dewberries, loganberries, pineapples, quinces, raspberries, rutabagas, spinach, strawberries, turnips and turnip greens, and youngberries. (tolerances for these items will be revoked if residue data and usage proposal are not submitted)
Processing data for residues of EPN in sugar beets, soybeans, tomatoes, citrus, prunes, grapes, apples, cottonseed, corn, and olives.
Residue data and tolerance proposals for bean vines and hay, sugar beet tops.

Special Processing Studies to provide:

Residue data for cooked (microwaving and boiling) sweet corn.
Residue data on fresh unwashed tomatoes
A washing study to provide residue data on lettuce

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